may frequently represent unrecognised outbreaks (Table 1).

Home-made food was the most important source of *S.* Enteritidis infection in this region, being implicated in 22 (81%) outbreaks and 134 (81.7%) sporadic infections. This rate is higher than that in some other reports [2,5]. If imperfect practice in kitchens has contributed to the striking increase in *S.* Enteritidis food poisoning in Bosnia and Herzegovina, this may be evidence that standards have declined in recent years, i.e., the post-war period.

For outbreaks in which the implicated food was investigated bacteriologically, and in those cases where epidemiological information regarding the suspected food was recorded, the main sources of infection were eggs and food containing eggs (33%), milk and milk products (22%), and minced beef (18%). Although this supports previous findings that eggs and egg products are the commonest vehicles of *S.* Enteritidis transmission [2,4], the large proportion of cases involving raw milk (22%) suggests that cattle from rural areas may represent an important source of infection. However, because of limited resources, food samples were examined from only five (19%) *S.* Enteritidis outbreaks during this 3-year period. Although the surveillance system for the sources of *S.* Enteritidis infections in this region is inadequate, this is also a problem in many other countries [1,2]. Medical staff in general practice should be strongly encouraged to report suspected cases to local public health authorities, and consistent criteria should be developed for their investigation.

REFERENCES

1. Lindqvist R, Andersson Y, Lindbäck J *et al.* A one-year study of foodborne illnesses in the municipality of Uppsala, Sweden. *Emerg Infect Dis* 2001; **7**: 588–592.
2. Caffer MI, Eiguer T. *Salmonella enteritidis* in Argentina. *Int J Food Microbiol* 1994; **21**: 15–19.
3. Kelly MT, Brenner DJ, Farmer. JJ. Enterobacteriaceae. In: Lennette EH, Balows A, Hausler WJ, Shadomy HJ, eds. *Manual of clinical microbiology*. Washington DC: American Society for Microbiology, 1985; 263–277.
4. Duguid JP, North RAE. Eggs and salmonella food-poisoning: an evaluation. *J Med Microbiol* 1991; **34**: 65–72.
5. Centers for Disease Control and Prevention. *Update on Salmonella serotype Enteritidis infections*. Atlanta: Centers for Disease Control and Prevention, 1999.

RESEARCH NOTE

Increasing incidence of resistance to nalidixic acid in shigellas from humans in England and Wales: implications for therapy

T. Cheasty, M. Day and E. J. Threlfall

Health Protection Agency, Specialist and Reference Microbiology Division, Laboratory of Enteric Pathogens, London, UK

ABSTRACT

Among shigellas isolated from patients in England and Wales in 2002, 10% of subgroups A, B and C, and 13% of subgroup D (*Shigella sonnei*), were resistant to nalidixic acid. As a consequence, should antimicrobial therapy be indicated, the efficacy of nalidixic acid as the preferred treatment for children with bacillary dysentery has been jeopardised.

Keywords Dysentery, nalidixic acid, quinolones, resistance, *Shigella*, therapy

Original Submission: 8 March 2004; **Revised Submission:** 20 May 2004; **Accepted:** 26 May 2004

Clin Microbiol Infect 2004; 10: 1033–1035
10.1111/j.1469-0691.2004.00982.x

The normal presentation of bacillary dysentery caused by *Shigella* isolates of subgroups A, B, C (*Shigella dysenteriae*, *S. flexneri*, *S. boydii*) and D (*S. sonnei*) is that of mild-to-moderate gastroenteritis. The disease is self-limiting, and the primary therapy is oral rehydration. However, symptoms can be severe in the very young, the very old, the malnourished and patients with other underlying diseases [1]. In such cases, administration of an effective antimicrobial agent should commence as soon as the clinical diagnosis is made. Ampicillin was the drug of choice until the mid-1980s [2], but this agent was compro-

Corresponding author and reprint requests: E. J. Threlfall, Heath Protection Agency, Specialist and Reference Microbiology Division, Laboratory of Enteric Pathogens, 61 Colindale Avenue, London NW9 5HT, UK
E-mail: john.threlfall@hpa.org.uk

mised by the widespread emergence of ampicillin-resistant strains [3] and was replaced by co-trimoxazole (trimethoprim–sulphamethoxazole) and nalidixic acid [4]. More recently, the American Public Health Association has recommended that, should antibiotic therapy be indicated for cases of acute shigellosis, oral co-trimoxazole, ciprofloxacin or ofloxacin should be used for treating adults, while oral co-trimoxazole, nalidixic acid or parenteral ceftriaxone should be used for treating children [5].

The Laboratory of Enteric Pathogens of the Health Protection Agency (London, UK) is the national reference centre for *Shigella* isolates from patients in England and Wales. Isolates are serotyped and tested for resistance to a range of therapeutic antimicrobial agents at the following levels (mg/L): ampicillin, 8; ceftriaxone, 1; trimethoprim, 2; nalidixic acid, 16; ciprofloxacin, 0.125 (= Cp_L) and 1.0 (= Cp_H) [6]. In 1998, following a comparative study of results with isolates received in the period 1978–1983, a substantive increase in the incidence of resistance to ampicillin and trimethoprim in isolates of subgroups A, B and C in the period 1995–1996 was reported [7]. Furthermore, *c*. 50% of *S. sonnei* (subgroup D) isolates were resistant to at least one of these antimicrobial agents, with 15% being resistant to both. In contrast, the incidence of resistance to nalidixic acid was low (0.5% for subgroups A, B and C, and 0.6% for subgroup D). High-level (clinical) resistance to ciprofloxacin (MIC ≥ 2 mg/L) was not detected. Based on these results, it was suggested that, if antimicrobial therapy was indicated, the best options would be nalidixic acid for children and a fluoroquinolone, such as ciprofloxacin or ofloxacin, for adults [7]. The present report documents the incidence of resistance to key therapeutic antimicrobial agents in isolates of subgroups A, B, C and D from patients in England and Wales in 2002.

In total, 912 isolates were studied, comprising 470 (52%) isolates of subgroups A (34), B (372) and C (64), and 442 (48%) isolates of subgroup D. In comparison to data from 1995–1996, the incidence of resistance to ampicillin had fallen in all subgroups, although a substantial proportion remained resistant (Table 1). In contrast, resistance to trimethoprim had increased by 9% in subgroups A, B and C, and by 35% in subgroup D, to the extent that >70% of all isolates were resistant. The most dramatic increase in resistance was observed in relation to nalidixic acid, with a 20-fold increase in resistance in subgroups A, B and C, and a 25-fold increase in subgroup D (Table 1). Furthermore, 14% of 77 *S. sonnei* isolates with resistance to nalidixic acid were from children aged <10 years. Resistance to ceftriaxone was not detected in isolates of any subgroup.

Table 1. Comparison of resistance (%) to therapeutic antimicrobial agents in isolates of *Shigella dysenteriae*, *S. flexneri*, *S. boydii* (subgroups A, B and C) and *S. sonnei* (subgroup D) from patients in England and Wales in 1995–1996 and 2002

	Subgroups A, B and C *S. dysenteriae*, *S. flexneri* and *S. boydii*		**Subgroup D *S. sonnei***	
Antimicrobial	**1995–1996 (*n* = 1524)**	**2002 (*n* = 470)**	**1996 (*n* = 1733)**	**2002 (*n* = 442)**
Ampicillin	65	57	42	31
Trimethoprim	64	73	53	88
Nalidixic acid[a]	0.5	10	0.5	13
Ceftriaxone	NT	0	NT	0

NT, not tested.
[a]All isolates resistant to nalidixic acid at 16 mg/L also exhibited decreased susceptibility to ciprofloxacin (MIC 0.25–1.0 mg/L). No isolate had a ciprofloxacin MIC >1.0 mg/L (= Cp_H).

These findings suggest that the efficacy of nalidixic acid as a preferred drug for the treatment of acute shigellosis in children in England and Wales has been jeopardised. Most (> 70%) patients infected with subgroups A, B and C had a history of recent foreign travel to developing countries. Nalidixic acid is used for prophylaxis in many developing countries, and it is possible that such usage has encouraged the development of resistance to this antimicrobial agent. However, the incidence of resistance to nalidixic acid has also increased 25-fold in isolates of subgroup D which, in >50% of cases, were from patients who had not travelled abroad. Thus, the development of resistance to nalidixic acid cannot result entirely from the imprudent use of this antimicrobial agent in developing countries.

All isolates of *Shigella* spp. with resistance to nalidixic acid also exhibited decreased susceptibility to ciprofloxacin (MIC 0.25–1.0 mg/L), although clinically significant resistance (MIC ≥2 mg/L) was not detected. Therefore, fluoroquinolone antibiotics, such as ciprofloxacin, may still be effective for the treatment of acute shigellosis in adults. However, physicians should be aware that treatment failures caused by strains with decreased susceptibility to ciprofloxacin have been reported for other enteric pathogens [8]. All isolates were sensitive to ceftriaxone in the

present investigation, and parenteral treatment with ceftriaxone has been suggested for children with shigellosis [5], although reservations have been expressed regarding both the cost of this antibiotic and the lack of an oral formulation [4].

Overall, these results demonstrated that the choice of an antimicrobial agent for the first-line treatment of shigellosis in England and Wales is becoming increasingly limited. Because of the increasing incidence of resistance to nalidixic acid, it is recommended strongly that isolates from children aged < 10 years should be tested for resistance before treatment is commenced. This recommendation is in line with information received from other countries, where in some instances nalidixic acid has now been abandoned as a therapeutic option for the treatment of acute shigellosis.

REFERENCES

1. Shears P, Hart CA. Gastrointestinal bacteria. In: Cook GC, ed. *Manson's tropical diseases*, 21st edn. Edinburgh: Saunders, 2003; 824–936.
2. Dupont HL. Shigella SP. Bacillary dysentery. In: Mandell GI, Douglas RG, Bennett JE, eds. *Principles and practice of infectious disease*, 2nd edn. New York: Churchill Livingstone, 1985; 1716–1722.
3. Gross RJ, Rowe B, Cheasty T, Thomas LV. Increase in drug resistance among *Shigella dysenteriae*, *Sh. flexneri and Sh. boydii*. *BMJ* 1981; **283**: 575–576.
4. Bennish ML, Salem MA. Rethinking options for the treatment of shigellosis. *J Antimicrob Chemother* 1992; **30**: 243–247.
5. Chin J, ed. *Control of communicable disease manual*, 17th edn. Washington DC: American Public Health Association, 2000.
6. Frost JA. Testing for resistance to antibacterial drugs. In: Chart H, ed. *Methods in practical laboratory bacteriology*. Boca Raton: CRC Press, 1994; 73–82.
7. Cheasty T, Skinner JA, Rowe B, Threlfall EJ. Increasing incidence of antibiotic resistance in shigellas from humans in England and Wales: recommendations for therapy. *Microb Drug Resist* 1998; **4**: 57–60.
8. Aarestrup F, Wiuff C, Mølbak K, Threlfall EJ. Is it time to change fluoroquinolone breakpoints for *Salmonella* spp.? *Antimicrob Agents Chemother* 2003; **47**: 827–829.